=> s l3 and (co(w)stimulat? or costimulat?)(P)(inhibit? or suppress? or modulat? or decreas? or antagoni?)

```
        232576 CO
         64679 STIMULAT?
           254 COSTIMULAT?
        278809 INHIBIT?
        136475 SUPPRESS?
        160501 MODULAT?
        650084 DECREAS?
         22680 ANTAGONI?
           191 (CO(W)STIMULAT? OR COSTIMULAT?)(P)(INHIBIT? OR SUPPRESS? OR
 MO
               DULAT? OR DECREAS? OR ANTAGONI?)
L5           0 L3 AND (CO(W)STIMULAT? OR COSTIMULAT?)(P)(INHIBIT? OR SUPPR
ESS
               ? OR MODULAT? OR DECREAS? OR ANTAGONI?)
```

=> s ccr5(P)(inhibit? or suppress? or antagoni? or decreas? or modulat? or treat? or therap?)

```
            10 CCR5
        278809 INHIBIT?
        136475 SUPPRESS?
         22680 ANTAGONI?
        650084 DECREAS?
        160501 MODULAT?
        599166 TREAT?
         92667 THERAP?
L6           4 CCR5(P)(INHIBIT? OR SUPPRESS? OR ANTAGONI? OR DECREAS? OR M
ODU
               LAT? OR TREAT? OR THERAP?)
```

=> d l6 1-4 date

L6: 1 of 4

TITLE: Methods and compositions for inhibiting HIV infection of cells by cleaving HIV co-receptor RNA
US PAT NO: 5,939,538 [IMAGE AVAILABLE] DATE ISSUED: Aug. 17, 1999
APPL-NO: 08/770,235 DATE FILED: Dec. 19, 1996

L6: 2 of 4

TITLE: Substituted aminoquinolines as modulators of chemokine receptor activity
US PAT NO: 5,919,776 [IMAGE AVAILABLE] DATE ISSUED: Jul. 6, 1999
APPL-NO: 08/993,494 DATE FILED: Dec. 18, 1997

L6: 3 of 4

TITLE: Kaposi's sarcoma-associated herpesvirus (KSHV) interleukin 6 (IL-6) and uses thereof
US PAT NO: 5,854,398 [IMAGE AVAILABLE] DATE ISSUED: Dec. 29, 1998
APPL-NO: 08/748,640 DATE FILED: Nov. 13, 1996
REL-US-DATA: Continuation-in-part of Ser. No. 686,349, Jul. 25, 1996.

L6: 4 of 4

TITLE: Polypeptides from Kaposi's sarcoma-associated herpesvirus, DNA enco[redacted]g same and uses thereof

US PAT NO: 5,849,564 [redacted] DATE ISSUED: Dec[redacted]5, 1998
[IMAGE AVAILABLE]

APPL-NO: 08/770,379 DATE FILED: Nov. 29, 1996

=> d l6 1-4 kwic

US PAT NO: 5,939,538 [IMAGE AVAILABLE] L6: 1 of 4

DETDESC:

DETD(147)

Ribozymes against **CCR5** which are stably expressed in the transformed PM1 cells and able to cleave **CCR5** mRNA efficiently to reduce the expression of **CCR5** on the cell surface **inhibits** cell-cell fusion. To ensure that the ribozyme is specific for **CCR5**, the fusion between the ribozyme-expressing PM1 cells and the HeLa cells expressing env derived from IHB (T-tropic) is examined. Ribozymes against **CCR5** do not effect IHB env dependent fusion.

DETDESC:

DETD(148)

After . . . quantitated by ELISA and used as an indicator for productive viral infection. The transformed PM1 cells which are negative for **CCR5**-dependent membrane fusion are resistant to infection by M-tropic (Bal, JRFL) but not T-tropic (LAV, IHB, RF) isolates. Once PM1 cells are transduced with AAV recombinant vectors encoding anti-**CCR5** ribozymes to protect the cells from the infection by M-tropic HIV-1 isolates, **inhibition** of **CCR5** expression in primary T lymphocytes and progenitor cells is verified.

US PAT NO: 5,919,776 [IMAGE AVAILABLE] L6: 2 of 4

SUMMARY:

BSUM(7)

Entry . . . (Nov. 14, 1996). The principal cofactor for entry mediated by the envelope glycoproteins of primary macrophage-trophic strains of HIV-1 is **CCR5**, a receptor for the .beta.-chemokines RANTES, MIP-1.alpha. and MIP-1.beta. (Deng, et al., Nature, 381, 661-666 (1996)). HIV attaches to the. . . molecule on the cell surface, and undergoes conformational changes which allow it to bind to another cell-surface receptor, such as **CCR5** and/or CXCR-4. This brings the viral envelope closer to the cell surface and allows interaction between gp41 on the viral. . . 667-673 (1996)). It has further been demonstrated that a complex of gp120 and soluble CD4 interacts specifically with CCR-5 and **inhibits** the binding of the natural CCR-5 ligands MIP-1.alpha. and MIP-1.beta. (Wu, et al., Nature, 384, 179-183 (1996); Trkola, et al.,. . .

SUMMARY:

BSUM(8)

Humans . . . of CCR-5 appears to confer protection from HIV-1 infection (Nature, 382, 668-669 (1996)). An inherited mutation in the gene for **CCR5**, Delta 32, has been shown to abolish functional expression of the gene and individuals homozygous for the mutation are apparently. . . genetic diversity of HIV-1 (Zhang, et al., Nature, 383, 768 (1996)). The .beta.-chemokine macrophage-derived chemokine (MDC)

has been shown to **inhibit** HIV-1 infection (Pal, et al., Science, 278 (5338), 695-698 (1997). T[redacted] chemokines RANTES, MIP-1.alpha., MIP-1.beta., vMIP-I, vMIP-II, SDF-1 ha[redacted] also been shown to **suppress** HI[redacted] A derivative of RANTES, (AOP)-RANTES, is a subnanomolar **antagonist** of CCR-5 function in monocytes (Simmons, et al., Science, 276, 276-279 (1997)). Monoclonal antibodies to CCR-5 have been reported to. . . in infected patients (see Science, 275, 1261-1264 (1997)). By focusing on the host's cellular immune response to HIV infection, better **therapies** towards all subtypes of HIV may be provided. These results indicate that **inhibition** of chemokine receptors presents a viable method for the prevention or **treatment** of infection by HIV and the prevention or **treatment** of AIDS.

US PAT NO: 5,854,398 [IMAGE AVAILABLE] L6: 3 of 4

DRAWING DESC:

DRWD(32)

FIG. . . . M23 HIV-1 strains and HIV-2 strain ROD/B in the presence or absence of vMIP-I. CCC/CD4 cells were transiently cotransfected with **CCR5** alone, **CCR5** plus empty pMET7 vector, **CCR5** plus vMIP-I in pMET7 vector, or **CCR5** plus the reverse orientation I-PIMv. The results after 72 hours of incubation with each retrovirus are expressed as a percentage of the foci forming units for cells transfected with **CCR5** alone. The forward vMIP-I construct **inhibited** NSI HIV-1 replication but not HIV-2 replication while the reverse I-PIMv construct had no effect on replication of any of. . .

DETDESC:

DETD(601)

Four . . . functionally active in B9 cell proliferation assays. It is primarily expressed in KSHV-infected hematopoietic cells rather than KS lesions. vMIP-I **inhibits** replication of **CCR5**-dependent HIV-1 strains in vitro indicating that it is functional and could contribute to interactions between these two viruses. Mimicry of. . .

DETDESC:

DETD(604)

The . . . 8-10 kDa .beta.-chemoattractant cytokines (chemokines) play an important role in virus infection-mediated inflammation (13). .beta.-chemokines are the natural ligand for **CCR5** and can block entry of non-syncytium inducing (NSI), primary lymphocyte and macrophage-tropic HIV-1 strains in vitro by binding to this. . . binding to specific interferon consensus sequences (ICS) within interferon-inducible promoter regions. A broad array of cellular responses to interferons is **modulated** by the repressor or transactivator functions of IRF proteins and several members (IRF-1 and IRF-2) have opposing anti-oncogenic and oncogenic. . .

DETDESC:

DETD(610)

To investigate whether the vMIP-I can **inhibit** NSI HIV-1 virus entry, human CD4+ cat kidney cells (CCC/CD4) were transiently transfected with plasmids expressing human **CCR5** and vMIP-I or its reverse construct I-PIMv (29). These cells were infected with either M23 or SF162 primary NSI HIV-1 isolates which are known to use **CCR5** as a co-receptor (30) or with the HIV-2 variant ROD/B which can infect CD4+ CCC cells without human **CCR5** (29, 30). Virus entry and replication was assayed by immunostaining for retroviral antigen production (FIG. 31). vMIP-I

cotransfection reduced NSI. . .

US PAT NO: 5,849,564 [IMAGE AVAILABLE] L6 of 4

DRAWING DESC:

DRWD(10)

FIG. . . . M23 HIV-1 strains and HIV-2 strain ROD/B in the presence or absence of vMIP-I. CCC/CD4 cells were transiently cotransfected with **CCR5** alone, **CCR5** plus empty pMET7 vector, **CCR5** plus vMIP-I in pMET7 vector, or **CCR5** plus the reverse orientation I-PIMv. The results after 72 hours of incubation with each retrovirus are expressed as a percentage of the foci forming units for cells transfected with **CCR5** alone. The forward vMIP-I construct **inhibited** NSI HIV-1 replication but not HIV-2 replication while the reverse I-PIMv construct had no effect on replication of any of. . .

DETDESC:

DETD(365)

Four . . . functionally active in B9 cell proliferation assays. It is primarily expressed in KSHV-infected hematopoietic cells rather than KS lesions. vMIP-I **inhibits** replication of **CCR5**-dependent HIV-1 strains in vitro indicating that it is functional and could contribute to interactions between these two viruses. Mimicry of. . .

DETDESC:

DETD(368)

The . . . an important role in virus infection-mediated inflammation (Cook et al., 1995, Science 269, 1583-1585). .beta.-chemokines are the natural ligand for **CCR5** and can block entry of non-syncytium inducing (NSI), primary lymphocyte and macrophage-tropic HIV-1 strains in vitro by binding to this. . . binding to specific interferon consensus sequences (ICS) within interferon-inducible promoter regions. A broad array of cellular responses to interferons is **modulated** by the repressor or transactivator functions of IRF polypeptides and several members (IRF-1 and IRF-2) have opposing anti-oncogenic and oncogenic. . .

DETDESC:

DETD(376)

To investigate whether the vMIP-I can **inhibit** NSI HIV-1 virus entry, human CD4+ cat kidney cells (CCC/CD4) were transiently transfected with plasmids expressing human **CCR5** and VMIP-I or its reverse construct I-PIMV (see **CCR5** and vMIP-I cloning in METHODS). These cells were infected with either M23 or SF162 primary NSI HIV-1 isolates which are known to use **CCR5** as a co-receptor (Clapham et al., 1992, J Virol 66, 3531-3537) or with the HIV-2 variant ROD/B which can infect. . .

s (cd28)(20n)(antibod?) and (inhibit? or suppress? or treat? or therap? or antagoni? or prevent? or block?)(20n)(hiv or hiv(w)1 or aids)

Processing
Processing
Processing
Processing
Processing
Processing
Processing
Processing

	8221	CD28
	1507497	ANTIBOD?
	1844	CD28(20N)ANTIBOD?
	2961173	INHIBIT?
	578326	SUPPRESS?
	4676874	TREAT?
	4402508	THERAP?
	783941	ANTAGONI?
	1477729	PREVENT?
	922519	BLOCK?
	243065	HIV
	243065	HIV
	7020615	1
	83882	HIV(W)1
	186267	AIDS
	104111	((((((INHIBIT? OR SUPPRESS?) OR TREAT?) OR THERAP?) OR ANTAGONI?) OR PREVENT?) OR BLOCK?)(20N)((HIV OR HIV(W)1) OR AIDS)
S3	50	(CD28)(20N)(ANTIBOD?) AND (INHIBIT? OR SUPPRESS? OR TREAT? OR THERAP? OR ANTAGONI? OR PREVENT? OR BLOCK?)(20N)(HIV OR HIV(W)1 OR AIDS)

? rd s3

...examined 50 records (50)
...completed examining records
S4 38 RD S3 (unique items)
? t s4/7/all

4/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12080170 BIOSIS NO.: 199900375019
Azodicarbonamide inhibits T-cell responses in vitro and in vivo.

AUTHOR: Tassignon Joel; Ismaili Jamila; Le Moine Alain; Van Laethem Francois; Leo Oberdan; Vandevelde Michel; Goldman Michel(a)
AUTHOR ADDRESS: (a)Laboratory of Experimental Immunology, Universite Libre de Bruxelles, 808, route de Lennik, B-10, Belgium

JOURNAL: Nature Medicine 5 (8):p947-950 Aug., 1999
ISSN: 1078-8956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Azodicarbonamide was recently identified as a new anti-**HIV**

agent that targets the zinc finger domains of the **HIV-1** NCp7 nucleocapsid protein. Here we demonstrate that azodicarbonamide **inhibits** in a dose-dependent manner the responses of purified human CD4+ T lymphocytes stimulated either by monoclonal **antibodies** against CD3 and **CD28** or by allogeneic dendritic cells. These suppressive effects involve a direct action on the calcium mobilization machinery, as azodicarbonamide strongly inhibited the calcium influx induced either by **antibodies** against CD3 and **CD28** or the chemokine RANTES, as well as by thapsigargin, an activator of depletion-activated calcium channels. In vivo, administration of azodicarbonamide into mice blunted their response to polyclonal T-cell activation induced by the injection of monoclonal antibody against CD3 and resulted in delayed rejection of skin allografts. In addition to its anti-**HIV** properties, azodicarbonamide is a new immunosuppressive agent that mighthave **therapeutic** applications in T cell-mediated inflammatory disorders.

4/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11755881 BIOSIS NO.: 199900001990
Development of an animal model for autotransfusion therapy: In vitro characterization and analysis of anti-CD3/CD28 expanded cells.

AUTHOR: Brice G T; Riley J L; Villinger F; Mayne A; Hillyer C D; June C H; Ansari A A(a)
AUTHOR ADDRESS: (a)Room B4107, Winship Cancer Cent., 1365B Clifton Rd. NE, Emory Univ. Sch. Med., Atlanta, GA 30322, USA

JOURNAL: Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 19 (3):p210-220 Nov. 1, 1998
ISSN: 1077-9450
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Previous studies have shown that in vitro culture of human CD4+ T cells with **antibodies** to CD3 and **CD28** immobilized on beads induced an antiviral effect to HIV-1 infection. Herein, we have used CD4+ T cells from nonhuman primates to address issues critical for use of such cells for **therapy** and immune reconstitution of humans and nonhuman primates infected with **HIV** and simian immunovirus (SIV). These studies include definition of the kinetics of the antiviral effect, the relative stability of the acquired phenotype, and whether such activated and expanded CD4+ T cells retain their immune function. Results of our studies show that antiviral effect is induced rapidly following activation with anti-CD3/CD28-coated beads. Additionally, the antiviral effect is not stable in these cells and requires continuous culture with anti-CD3/CD28 beads. Removal of CD4+ T cells from anti-CD3/CD28 stimulation renders these cells susceptible to infection, demonstrating that the resistant phenotype is not stable in these cultures. However, anti-CD3/CD28 expanded CD4+ T cells do retain immune function. Thus, although these findings imply a note of caution for therapeutic strategies aimed at providing patients with virus-resistant CD4+ T cells, the present study suggests that transfusion of such cells with retained immune function may have immune restoration capability.

4/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11253349 BIOSIS NO.: 199800034681
Recovery of replication-competent **HIV** despite prolonged

suppression of plasma viremia.

AUTHOR: Wong Joseph K(a); [redacted]ezareh Marjan; Guenthard Huldrych F; Havlir Diane V; Ignacio Caroline C; Spina Celsa A; Richman Douglas D
AUTHOR ADDRESS: (a)Dep. Med., Univ. Calif. San Diego, Sch. Med., 9500 Gilman Drive, La Jolla, CA 92093, USA

JOURNAL: Science (Washington D C) 278 (5341):p1291-1295 Nov. 14, 1997
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In evaluating current combination drug regimens for **treatment** of human immunodeficiency virus (**HIV**) disease, it is important to determine the existence of viral reservoirs. After depletion of CD8 cells from the peripheral blood mononuclear cells (PBMCs) of both patients and normal donors, activation of patient CD4 lymphocytes with immobilized **antibodies** to CD3 and **CD28** enabled the isolation of virus from PBMCs of six patients despite the **suppression** of their plasma **HIV** RNA to fewer than 50 copies per milliliter for up to 2 years. Partial sequencing of **HIV** pol revealed no new drug resistance mutations or discernible evolution, providing evidence for viral latency rather than drug failure.

4/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10532804 BIOSIS NO.: 199699153949
Reversal of the **inhibitory** effects of **HIV**-gp120 on CD4+ T cells by stimulation through the CD28 pathway.

AUTHOR: Faith A(a); Yssel H; O'Hehir R E; Lamb J R
AUTHOR ADDRESS: (a)SIAF, Obere Strasse 22, CH-7270 Davos, Switzerland

JOURNAL: Clinical and Experimental Immunology 105 (2):p225-230 1996
ISSN: 0009-9104
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effects of exposure to HIV-gp 120 on proliferation and cytokine production by T cell lines were investigated. T cell lines were generated by stimulation of peripheral blood mononuclear cells from several healthy donors with cross-linked anti-CD3 antibodies and IL-2. These T cell lines exhibited the characteristics of Th1 cells, producing IL-2 and interferon-gamma (IFN-gamma), but not IL-4, on stimulation with anti-CD3 antibodies. In the presence of gp120, stimulation with anti-CD3 antibodies was inhibited in terms of both proliferative responses and the secretion of IL-2 and IFN-gamma. Similar effects were observed when a T cell line was stimulated in the presence of a synthetic peptide representing the CD4-binding region of gp 120. Neither gp 1 20 nor the CD4-binding region peptide had any effect on IL-4 production by the T cell lines. Stimulation through the **CD28** pathway partially restored both the proliferative effect and cytokine production by T cell lines in response to anti-CD3 **antibodies** in the presence of gp120. Anti-**CD28 antibodies** also partially restored cytokine production when purified CD4+ T cells from a T cell line were stimulated with anti-CD3 antibodies in the presence of gp120. Anti-gp120 **antibodies** partially or completely reversed the inhibitory effects of gp120 on T cell proliferation. These results indicate that stimulation through the **CD28** pathway may restore defective CD4+ T cell responses in HIV-infected individuals.

4/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10468297 BIOSIS NO.: 199699089442
Antiviral effect and ex vivo CD4+ T cell proliferation in HIV-positive patients as a result of CD28 costimulation.

AUTHOR: Levine Bruce L; Mosca Joseph D; Riley James L; Carroll Richard G; Vahey Maryanne T; Jagodzinski Linda L; Wagner Kenneth F; Mayers Douglas L ; Burke Donald S; Weislow Owen S; Louis Daniel C S; June Carl H(a)
AUTHOR ADDRESS: (a)Naval Med. Res. Inst., Bethesda, MD 20889, USA

JOURNAL: Science (Washington D C) 272 (5270):p1939-1943 1996
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Because stimulation of CD4+ lymphocytes leads to activation of human immunodeficiency virus-type 1 (**HIV-1**) replication, viral spread, and cell death, adoptive CD4+ T cell **therapy** has not been possible. When antigen and **CD28** receptors on cultured T cells were stimulated by monoclonal **antibodies** (mAbs) to CD3 and **CD28** that had been immobilized, there was an increase in the number of polyclonal CD4+ T cells from HIV-infected donors. Activated cells predominantly secreted cytokines associated with T helper cell type 1 function. The HIV-1 viral load declined in the absence of antiretroviral agents. Moreover, CD28 stimulation of CD4+ T cells from uninfected donors rendered these cells highly resistant to **HIV-1** infection. Immobilization of CD28 mAb was crucial to the development of **HIV** resistance, as cells stimulated with soluble CD28 mAb were highly susceptible to **HIV** infection. The CD28-mediated antiviral effect occurred early in the viral life cycle, before **HIV-1** DNA integration. These data may facilitate immune reconstitution and gene **therapy** approaches in persons with **HIV** infection.

4/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10225176 BIOSIS NO.: 199698680094
The Fas receptor in HIV infection: Expression on peripheral blood lymphocytes and role in the depletion of T cells.

AUTHOR: Gehri Roland; Hahn Sinuhe; Rothen Madeleine; Steuerwald Michael; Nuesch Reto; Erb Peter
AUTHOR ADDRESS: Inst. Med. Microbiol., Univ. Basel, Petersplatz 10, CH-4003 Basel, Switzerland

JOURNAL: AIDS (Philadelphia) 10 (1):p9-16 1996
ISSN: 0269-9370
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective: To analyse the role of the apoptosis-inducing Fas receptor in the depletion of CD4+ and CD8+ T cells in **HIV**-infected individuals. Methods: Peripheral blood lymphocytes (PBL) obtained from **HIV**-infected subjects of all 1993 Centers for Disease Control and **Prevention** (CDC) stages and from non-infected controls were examined. A two-colour cytofluorometry was employed using monoclonal **antibodies** against Fas receptor (CD95) in combination with the surface markers CD4, CD8, **CD28**, CD26 and CD45RO. CD4+ and CD8+

T-cell-enriched PBL were used as target cells to assess their susceptibility to lysis by CD4+ cytotoxic T lymphocytes (CTL) which kill via the Fas pathway. Results: Fas+ PBL are more elevated in HIV-infected individuals than in HIV-negative controls and increase significantly from CDC stages A to C. Whereas Fas+CD4+ and Fas-CD4+ T-cell populations decline in parallel with the progression of HIV infection, the Fas+CD8+, but not of the Fas-CD8+ fraction, significantly increases. The Fas+CD8+ lymphocytes are susceptible to Fas-mediated lysis as they are efficiently killed by Fas-ligand+CD4+ CTL. Conclusion: The Fas receptor may contribute, but not as a unique cause, to the decline of CD4+ T cells in HIV-infected individuals. This and the significant increase of the number of Fas+CD8+ T cells indicates that Fas-mediated immune regulation is disturbed.

4/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08091030 BIOSIS NO.: 000093101103
ACTIVATION-INDUCED DEATH BY APOPTOSIS IN CD4-POSITIVE T CELLS FROM HUMAN IMMUNODEFICIENCY VIRUS-INFECTED ASYMPTOMATIC INDIVIDUALS

AUTHOR: GROUX H; TORPIER G; MONTE D; MOUTON Y; CAPRON A; AMEISEN J C
AUTHOR ADDRESS: UNITE MIXTE INSERM U167-CNRS 624, INST. PASTEUR, 1, RUE DU PR. CALMETTE, 59019 LILLE, FRANCE.

JOURNAL: J EXP MED 175 (2). 1992. 331-340.
FULL JOURNAL NAME: Journal of Experimental Medicine
CODEN: JEMEA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: In immature thymocytes, T cell receptor for antigen (TCR) mobilization lead to an active T cell suicide process, apoptosis, which is involved in the selection of the T cell repertoire. We have proposed that inappropriate induction of such a cell death program in the mature CD4+ T cell population could account for both early qualitative and late quantitative CD4+ T lymphocyte defects of human immunodeficiency virus (HIV)-infected individuals (Ameisen, J.C. and A. Capron. 1991. Immunol. Today. 4:102). Here, we report that the selective failure of CD4+ T cells from 59 clinically asymptomatic HIV-infected individuals to proliferate in vitro to TCR mobilization by major histocompatibiity complex class II-dependent superantigens and to pokeweed mitogen (PWM) is due to an active CD4+ T cell death process, with the biochemical and ultrastructural features of apoptosis. Activation-induced cell death occurred only in the CD4+ T cell population from HIV-infected asymptomatic individuals and was not observed in T cells from any of 58 **HIV**-seronegative controls, including nine patients with other acute or chronic infectious diseases. Activation-induced CD4+ T cell death was **prevented** by cycloheximide, cyclosporin A, and a **CD28** monoclonal **antibody** (mAb). The **CD28** mAb not only prevented apoptosis but also restored T cell proliferation to stimuli, including PWM, superantigens, and the tetanus and influenza recall antigens. These findings may have implications for the understanding of the pathogenesis of acquired immune deficiency syndrome and for the design of specific therapeutic strategies.

4/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07866446 BIOSIS NO.: 000092125812
MODULATION OF T-CELL ACTIVATION THROUGH PROTEIN KINASE C-DEPENDENT OR A-DEPENDENT SIGNALLING PATHWAYS SYNERGISTICALLY INCREASES HUMAN

IMMUNODEFICIENCY VIRUS LONG TERMINAL REPEAT INDUCTION BY CYTOMEGALOVIRUS IMMEDIATE-EARLY PROTEINS

AUTHOR: PAYA C V; VIRELIZIER J-L; MICHELSON S
AUTHOR ADDRESS: UNITE IMMUNOL. VIRALE, DEP. DES RETROVIRUS, INST. PASTEUR, 75724 PARIS CEDEX 15, FR.

JOURNAL: J VIROL 65 (10). 1991. 5477-5484.
FULL JOURNAL NAME: Journal of Virology
CODEN: JOVIA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: By using human CD4+ lymphoblastoid T cells transiently cotransfected with human immunodeficiency virus (HIV) and cytomegalovirus (CMV), we tested whether modulation of T-cell activation through the protein kinase C (PKC) or the protein kinase A (PKA) pathway synergized with CMV immediate-early (IE) proteins in HIV long terminal repeat (LTR) transactivation. Stimulation with phorbol myristate acetate, tumor necrosis factor, or cross-linked **antibodies** to CD3 and **CD28** resulted in modest enhancement (two- to fourfold) of the activity of a luciferase expression vector under control of the HIV LTR. Cotransfection of a vector expression the CMV IE1 and IE2 proteins under the control of their own promoter enhanced HIV LTR activity 16- to 49-fold. Combination of any one of the above stimuli and CMV IE expression amplified HIV LTR activity 99- to 624-fold. Stimulation of PKA-dependent pathways with forskolin, 8-bromo cyclic AMP, or prostaglandin E2 had a minimal effect on HIV LTR activity, whereas such stimuli resulted in synergistic amplification in cells cotransfected with CMV IE (three- to fivefold increases over the effects of CMV IE alone). This synergism was independent of the NF-.kappa.B binding motifs within the HIV LTR. CMV IE2, but not IE1, protein induced HIV transactivation and synergized with signals modulating T-cell activation. The intense synergism observed was superior to the increase in IE protein expression following PKC activation by phorbol myristate acetate. **Treatment** of cells with PKC **inhibitor** GF109203X **blocked** most of the observed synergism. These results show that stimulation of transduction pathways normally unable to induce **HIV** LTR transcription may become effective in cells doubly infected with HIV and CMV. Furthermore, our results imply that a cellular factor(s) or phosphorylation events induced during cell activation are important for full transactivating efficiency of CMV IE proteins on HIV LTR transactivation.

4/7/9 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07543517 EMBASE No: 1999038609
Immune restoration does not invariably occur following long-term **HIV-1 suppression** during antiretroviral **therapy**

Pakker N.G.; Kroon E.D.M.B.; Roos M.T.L.; Otto S.A.; Hall D.; Wit F.W.N.M.; Hamann D.; Van der Ende M.E.; Claessen F.A.P.; Kauffmann R.H.; Koopmans P.P.; Kroon F.P.; Ten Napel C.H.H.; Sprenger H.G.; Weigel H.M.; Montaner J.S.G.; Lange J.M.A.; Reiss P.; Schellekens P.T.A.; Miedema F.
F. Miedema, CLB, Sanquin, Dept. of Clinical Viro-Immunology, Plesmanlaan 125, 1066 CX Amsterdam Netherlands
AIDS (AIDS) (United Kingdom) 1999, 13/2 (203-212)

CODEN: AIDSE ISSN: 0269-9370
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 37

Background: Current antiretroviral **treatment** can induce significant and sustained virological and immunological responses in **HIV-1**

-infected persons over at least the short- to mid-term. Objectives: In this study, long-term immune reconstitution was investigated during highly active antiretroviral therapy. Methods: Patients enrolled in the INCAS study in The Netherlands were treated for 102 weeks (range 52-144 weeks) with nevirapine (NVP) + zidovudine(ZDV) (n = 9), didanosine (ddl) + ZDV (n = 10), or NVP + ddl + ZDV (n = 10). Memory and naive CD4+ and CD8+ T cells were measured using CD45RA and CD27 monoclonal **antibodies** (mAb), T-cell function was assayed by CD3 + **CD28** mAb stimulation, and plasma HIV-1 RNA load was measured by ultra-direct assay (cut-off < 20 copies/ml). Results: Compared to both double combination regimens the triple combination regimen resulted in the most sustained increase in CD4+ T cells (change in CD4+, + 253 x 10sup 6 cells/l; standard error, 79 x 10sup 6 cells/l) and reduction of plasma HIV-1 RNA. In nine patients (31%) (ddl + ZDV, n = 2; NVP + ddl + ZDV, n = 7) plasma HIV-1 RNA levels remained below cut-off for at least 2 years. On average, these long-term virological responders demonstrated a significantly higher increase of naive and memory CD4+ T cells (P = 0.01 and 0.02, respectively) as compared with patients with a virological failure, and showed improved T-cell function and normalization of the naive: memory CD8+ T-cell ratio. However, individual virological success or failure did not predict the degree of immunological response. T-cell patterns were independent of baseline CD4+ T-cell count, T-cell function, HIV-1 RNA load or age. Low numbers of naive CD4+ T cells at baseline resulted in modest long-term naive T-cell recovery. Conclusions: Patient with prolonged undetectable plasma **HIV-1** RNA levels during antiretroviral **therapy** do not invariably show immune restoration. Naive T-cell recovery in the setting of complete viral suppression is a gradual process, similar to that reported for immune recovery in adults after chemotherapy and bone marrow transplantation.

4/7/10 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07515153 EMBASE No: 1998422051
Role of 4-1BB in immune responses
Vinay D.S.; Kwon B.S.
D.S. Vinay, Indiana University School Medicine, Indianapolis, IN 46202 United States
Seminars in Immunology (SEMIN. IMMUNOL.) (United Kingdom) 1998, 10/6 (481-489)

CODEN: SEIME ISSN: 1044-5323
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 43

4-1BB is an inducible T cell surface receptor which belongs to the tumor necrosis factor receptor superfamily, a group of cysteine-rich cell-surface molecules. Both human and mouse 4-1BB recently received HLDA nomenclature. Naive T cells lack 4-1BB, which is not only induced upon T cell activation, but also remains on activated T cells. The natural ligand for 4-1BB, 4-1BBL is also induced and is found on activated antigen-presenting cells. Cross-linking of the 4-1BB molecule by agonistic antibody transmits a distinct and potent co-stimulatory signal leading to the activation and differentiation of CD4sup + and CD8sup + cells. 4-1BB transmits signals through the TRAF2-NIK pathway and activates NF-kappaB. Signals relayed through 4-1BB inhibit activation-induced cell death and rescue the immune system during the post-**CD28** phase. **Antibodies** to the 4-1BB molecule can increase GVHD, accelerate the rejection of cardiac allograft and skin transplants, and eradicate established tumors. Interference with the 4-IBB-4-1BBL pathway may be of **therapeutic** use in the **treatment** of **HIV** infection. 4-1BB-deficient mice show dysregulated immune responses and mount elevated Ig responses to T-dependent antigens.

4/7/11 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07424369 EMBASE No: 1998333533
Immunologic effects of combined protease **inhibitor** and reverse transcriptase **inhibitor therapy** in previously **treated** chronic **HIV-1** infection
Giorgi J.V.; Majchrowicz M.A.; Johnson T.D.; Hultin P.; Matud J.; Detels R.
Dr. J.V. Giorgi, UCLA School of Medicine, 12-240 Factor Building, 10833 Le Conte Avenue, Los Angeles, CA 90095-1745 United States
AIDS (AIDS) (United Kingdom) 01 OCT 1998, 12/14 (1833-1844)

CODEN: AIDSE ISSN: 0269-9370
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 49

Objective: To evaluate the efficacy of combination protease and reverse transcriptase **inhibitor therapy** in correcting **HIV-1** -induced lymphocyte subset abnormalities in previously **treated** adults. Design: A 48-week observational study of lymphocyte subsets in 12 participants in the Multicenter **AIDS** Cohort Study who were already taking at least one reverse transcriptase **inhibitor** and added a protease **inhibitor** to their **treatment** regimen. Comparison groups were **HIV**-seronegative homosexual men, **HIV**-seronegative heterosexual men, and homosexual **HIV-1**-infected men who were long-term non-progressors. Methods: Three-color immunofluorescence and monoclonal antibodies were used to assess **HIV-1**-induced lymphocyte subset alterations related to immune deficiency and immune activation. Plasma **HIV-1** RNA levels were monitored to assess **suppression** of viral replication. Results: CD4+ cell counts significantly increased and lymphocyte activation measured as CD38 and HLA-DR expression on CD8+ T cells significantly decreased by 48 weeks. CD4+ cell values remained abnormal even in those who were fully suppressed. Some T-cell activation markers decreased to levels observed in long-term non-progressors. The increase in CD4+ T-cell numbers reached a plateau by week 24, but the increase in resting HLA-DR- CD38- T cells was sustained through week 48. Proportions of CD45RA+ CD62L-selectin+ and CD28+ CD4+ T-cell subsets and Fas expression were not abnormal at baseline compared with seronegative homosexual controls. Conclusions: The most significant impact of suppression of viral replication was reversal of T-cell activation. However, normalization of lymphocyte subset perturbations associated with chronic **HIV-1** infection was not achieved after 1 year of **treatment** with current combination antiretroviral regimens. More profound viral **suppression, therapy** for longer than 1 year, or immunologic augmentation may be needed to fully reverse the abnormalities.

4/7/12 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

06563958 EMBASE No: 1996225026
Reversal of the **inhibitory** effects of **HIV**-gp120 on CD4sup + T cells by stimulation through the CD28 pathway
Faith A.; Yssel H.; O'Hehir R.E.; Lamb J.R.
SIAF, Obere Strasse 22,CH-7270 Davos Switzerland
Clinical and Experimental Immunology (CLIN. EXP. IMMUNOL.) (United Kingdom) 1996, 105/2 (225-230)

CODEN: CEXIA ISSN: 0009-9104
DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The effects of exposure [redacted] HIV-gp 120 on proliferation a[redacted] cytokine production by T cell lines were investigated. T cell lines were generated by stimulation of peripheral blood mononuclear cells from several healthy donors with cross-linked anti-CD3 antibodies and IL-2. These T cell lines exhibited the characteristics of Th1 cells, producing IL-2 and interferon-gamma (IFN-gamma), but not IL-4, on stimulation with anti-CD3 antibodies. In the presence of gp120, stimulation with anti-CD3 antibodies was inhibited in terms of both proliferative responses and the secretion of IL-2 and IFN-gamma. Similar effects were observed when a T cell line was stimulated in the presence of a synthetic peptide representing the CD4-binding region of gp120. Neither gp120 nor the CD4-binding region peptide had any effect on IL-4 production by the T cell lines. Stimulation through the **CD28** pathway partially restored both the proliferative effect and cytokine production by T cell lines in response to anti-CD3 **antibodies** in the presence of gp120. Anti-**CD28 antibodies** also partially restored cytokine production when purified CD4sup + T cells from a T cell line were stimulated with anti-CD3 antibodies in the presence of gp120. Anti-gp120 **antibodies** partially or completely reversed the inhibitory effects of gp120 on T cell proliferation. These results indicate that stimulation through the **CD28** pathway may restore defective CD4sup + T cell responses in HIV-infected individuals.

4/7/13 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

06552092 EMBASE No: 1996212681
Antiviral effect and ex vivo CD4sup + T cell proliferation in HIV-positive patients as a result of CD28 costimulation
Levine B.L.; Mosca J.D.; Riley J.L.; Carroll R.G.; Vahey M.T.; Jagodzinski L.L.; Wagner K.F.; Mayers D.L.; Burke D.S.; Weislow O.S.; St. Louis D.C.; June C.H.
Naval Medical Research Institute,Bethesda, MD 20889 United States
Science (SCIENCE) (United States) 1996, 272/5270 (1939-1943)

CODEN: SCIEA ISSN: 0036-8075
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Because stimulation of CD4sup + lymphocytes leads to activation of human immunodeficiency virus-type 1 (**HIV-1**) replication, viral spread, and cell death, adoptive CD4sup + T cell **therapy** has not been possible. When antigen and **CD28** receptors on cultured T cells were stimulated by monoclonal **antibodies** (mAbs) to CD3 and **CD28** that had been immobilized, there was an increase in the number of polyclonal CD4sup + T cells from HIV-infected donors. Activated cells predominantly secreted cytokines associated with T helper cell type 1 function. The HIV-1 vital load declined in the absence of antiretroviral agents. Moreover, CD28 stimulation of CD4sup + T cells from uninfected donors rendered these cells highly resistant to **HIV-1** infection. Immobilization of CD28 mAb was crucial to the development of **HIV** resistance, as cells stimulated with soluble CD28 mAb were highly susceptible to **HIV** infection. The CD28-mediated antiviral effect occurred early in the viral life cycle, before **HIV-1** DNA integration. These data may facilitate immune reconstitution and gene **therapy** approaches in persons with **HIV** infection.

4/7/14 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

06357753 EMBASE No: 1996022193

The Fas receptor in HIV infection: Expression on peripheral blood lymphocytes and role in the depletion of T cells

Gehri P.; Hahn S.; Rothe M.; Steuerwald M.; Nuesch R.; [redacted] P.
Institute for Medical Microbiology, University of Basel, Petersplatz 10,CH-4003 Basel Switzerland

AIDS (AIDS) (United Kingdom) 1996, 10/1 (9-16)

CODEN: AIDSE ISSN: 0269-9370
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Objective: To analyse the role of the apoptosis-inducing Fas receptor in the depletion of CD4+ and CD8+ T cells in **HIV**-infected individuals. Methods: Peripheral blood lymphocytes (PBL) obtained from **HIV** -infected subjects of all 1993 Centers for Disease Control and **Prevention** (CDC) stages and from non-infected controls were examined. A two-colour cytofluorometry was employed using monoclonal **antibodies** against Fas receptor (CD95) in combination with the surface markers CD4, CD8, **CD28**, CD26 and CD45RO. CD4+ and CD8+ T-cell-enriched PBL were used as target cells to assess their susceptibility to lysis by CD4+ cytotoxic T lymphocytes (CTL) which kill via the Fas pathway. Results: Fas+ PBL are more elevated in HIV-infected individuals than in HIV-negative controls and increase significantly from CDC stages A to C. Whereas Fas+ CD4+ and Fas-CD4+ T-cell populations decline in parallel with the progression of HIV infection, the Fas+CD8+, but not of the Fas-CD8+ fraction, significantly increases. The Fas+ CD8+ lymphocytes are susceptible to Fas-mediated lysis as they are efficiently killed by Fas-ligand+CD4+CTL. Conclusion: The Fas receptor may contribute, but not as a unique cause, to the decline of CD4+ T cells in HIV-infected individuals. This and the significant increase of the number of Fas+ CD8+ T cells indicates that Fas-mediated immune regulation is disturbed.

4/7/15 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

06199937 EMBASE No: 1995216147
Role of B70/B7-2 in CD4sup + T-cell immune responses induced by dendritic cells

Fagnoni F.F.; Takamizawa M.; Godfrey W.R.; Rivas A.; Azuma M.; Okumura K.; Engleman E.G.
Stanford Medical School Blood Center, 800 Welch Road,Palo Alto, CA 94304 United States

Immunology (IMMUNOLOGY) (United Kingdom) 1995, 85/3 (467-474)

CODEN: IMMUA ISSN: 0019-2805
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Dendritic cells (DC) are potent antigen-presenting cells (APC). However, the molecular basis underlying this activity remains incompletely understood. To address this question, we generated murine monoclonal antibodies (mAb) against human peripheral blood-derived DC. One such antibody, designated IT209, stained differentiated DC and adherent monocytes, but failed to stain freshly isolated peripheral blood mononuclear cells (PBMC). The antigen recognized by IT209 was identified as B70 (B7-2; also recently identified as CD86). Using this mAb we studied the role of B70 in CD4sup + T-cell activation by DC in vitro. IT209 partly inhibited the proliferative response of CD4sup + T cells to allogeneic DC and to recall antigens, such as tetanus toxoid (TT) and purified protein derivative (PPD) of tuberculin, presented by autologous DC. More importantly, the mAb had a potent **inhibitory** effect on the primary response of CD4sup + T cells to autologous DC pulsed with human immunodeficiency virus (**HIV**) gp160 or keyhole limpet haemocyanin (KLH). Adherent monocytes, despite their expression of B70, failed to

induce T-cell responses to these antigens. IT209-mediated inhibition of CD4sup + T-cell responses was equivalent to that produced by anti-CD28 mAb, whereas an anti-CD80 mAb was only marginally inhibitory and did not augment the effect of IT209. These findings indicate that the B70 antigen plays an important role in DC-dependent CD4sup + T-cell activation, particularly in the induction of primary CD4sup + T-cell responses to soluble antigens. However, since activated monocytes, despite their expression of B70, failed to prime naive T cells to these antigens, our results suggest that additional molecules contribute to the functions of DC in CD4sup + T-cell activation.

4/7/16 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE

05417976 EMBASE No: 1993186075
Regulation of HIV production by blood mononuclear cells from HIV-infected donors: II. HIV-1 production depends on T cell-monocyte interaction
Diegel M.L.; Moran P.A.; Gilliland L.K.; Damle N.K.; Hayden M.S.; Zarling J.M.; Ledbetter J.A.
Bristol-Myers Squibb, Pharmaceutical Research Institute, 3005 First Avenue,Seattle, WA 98121 United States
AIDS Research and Human Retroviruses (AIDS RES. HUM. RETROVIRUSES) (United States) 1993, 9/5 (465-473)

CODEN: ARHRE ISSN: 0889-2229
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Cell-cell interactions induced between T cells and monocytes by certain soluble anti-CD3 monoclonal antibodies (MAbs) were previously shown to be required for high-level production of HIV-1 by peripheral blood mononuclear cells (PBMCs) from infected donors. Staphylococcal enterotoxin or superantigen (SAg) is another mitogen inducing monocytes-T cell interactions that exhibit potent induction of HIV-1 production. Antibodies to several adhesion molecules were used to test the requirements for T cell- and monocyte-associated adhesion molecules in HIV-1 production following activation with anti-CD3 or SAg. **Blocking** of either CD2-LFA-3, or CD18-ICAM-1, **inhibited** anti-CD3- or SAg-induced **HIV-1** production by more than 90% without **inhibiting** CD4sup + T cell proliferation. **Inhibition** of **HIV** production was observed when either the T cell or monocyte coreceptor was bound by MAbs to these adhesion molecules. **Blocking** of CD28-B7 interactions by soluble CTLA-4 fusion protein, a CD28 homolog, **inhibited** both **HIV-1** production and CD4sup + T cell proliferation. Fc binding was not required for **HIV-1 inhibition** by MAbs to CD2 and CD18, because Fab or F(ab')inf 2 fragments of these MAbs **inhibited HIV-1** production by more than 80%. A chimeric single-chain MAb to CD2 was produced, containing heavy and light chain variable regions from MAb 35.1 to CD2 linked to the constant regions of human IgGinf 1 (CD2 SFv-Ig). This humanized CD2 SFv-Ig **inhibited HIV-1** production by 30% to >98 %. These results thus indicate that simultaneous engagement of multiple adhesion pathways between T cells and monocytes are required for **HIV** production by patients PBMCs and may have implications for **therapy** of **HIV** infections.

4/7/17 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE

04920788 EMBASE No: 1992061004
Activation-induced death by apoptosis in CD4sup + T cells from human immunodeficiency virus-infected asymptomatic individuals
Groux H.; Torpier G.; Monte D.; Mouton Y.; Capron A.; Ameisen J.C.

Unite mixte INSERM, U167-CNRS 624, Institut Pasteur, 1, rue du Pr. Calmette,59019 Lille France
Journal of Experimental Medicine (J. EXP. MED.) (United States) 1992, 175/2 (331-340)

CODEN: JEMEA ISSN: 0022-1007
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

In immature thymocytes, T cell receptor for antigen (TCR) mobilization leads to an active T cell suicide process, apoptosis, which is involved in the selection of the T cell repertoire. We have proposed that inappropriate induction of such a cell death program in the mature CD4sup + T cell population could account for both early qualitative and late quantitative CD4sup + T lymphocyte defects of human immunodeficiency virus (HIV)-infected individuals (Ameisen, J. C., and A. Capron. 1991. Immunol. Today. 4:102). Here, we report that the selective failure of CD4sup + T cells from 59 clinically asymptomatic HIV-infected individuals to proliferate in vitro to TCR mobilization by major histocompatibility complex class II-dependent superantigens and to pokeweed mitogen (PWM) is due to an active CD4sup + T cell death process, with the biochemical and ultrastructural features of apoptosis. Activation-induced cell death occurred only in the CD4sup + T cell population from HIV-infected asymptomatic individuals and was not observed in T cells from any of 58 **HIV-** seronegative controls, including nine patients with other acute or chronic infectious diseases. Activation-induced CD4sup + T cell death was **prevented** by cycloheximide, cyclosporin A, and a **CD28** monoclonal **antibody** (mAb). The **CD28** mAb not only prevented apoptosis but also restored T cell proliferation to stimuli, including PWM, superantigens, and the tetanus and influenza recall antigens. These findings may have implications for the understanding of the pathogenesis of acquired immune deficiency syndrome and for the design of specific therapeutic strategies.

4/7/18 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE

04835587 EMBASE No: 1991330323
Modulation of T-cell activation through protein kinase C- or A-dependent signalling pathways synergistically increases human immunodeficiency virus long terminal repeat induction by cytomegalovirus immediate-early proteins
Paya C.V.; Virelizier J.-L.; Michelson S.
Unite d'Immunologie Virale, Departement des Retrovirus, Institut Pasteur,75724 Paris Cedex 15 France
Journal of Virology (J. VIROL.) (United States) 1991, 65/10 (5477-5484)

CODEN: JOVIA ISSN: 0022-538X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

By using human CD4sup + lymphoblastoid T cells transiently cotransfected with human immunodeficiency virus (HIV) and cytomegalovirus (CMV), we tested whether modulation of T-cell activation through the protein kinase C (PKC) or the protein kinase A (PKA) pathway synergized with CMV immediate-early (IE) proteins in HIV long terminal repeat (LTR) transactivation. Stimulation with phorbol myristate·acetate, tumor necrosis factor, or cross-linked **antibodies** to CD3 and **CD28** resulted in modest enhancement (two- to fourfold) of the activity of a luciferase expression vector under control of the HIV LTR. Cotransfection of a vector expressing the CMV IE1 and IE2 proteins under the control of their own promoter enhanced HIV LTR activity 16- to 49-fold. Combination of any one of the above stimuli and CMV IE expression amplified HIV LTR activity 99- to 624-fold. Stimulation of PKA-dependent pathways with forskolin, 8-bromo

cyclic AMP, or prostaglandin E2 had a minimal effect on HIV LTR activity, whereas such stimuli resulted in synergistic amplification in cells cotransfected with CMV IE (three- to fivefold increases over the effects of CMV IE alone). This synergism was independent of the NF-kappaB binding motifs within the HIV LTR. CMV IE2, but not IE1, protein induced HIV transactivation and synergized with signals modulating T-cell activation. The intense synergism observed was superior to the increase in IE protein expression following PKC activation by phorbol myristate acetate. **Treatment** of cells with PKC **inhibitor** GF109203X **blocked** most of the observed synergism. These results show that stimulation of transduction pathways normally unable to induce **HIV** LTR transcription may become effective in cells doubly infected with HIV and CMV. Furthermore, our results imply that a cellular factor(s) or phosphorylation events induced during cell activation are important for full transactivating efficiency of CMV IE proteins on HIV LTR transactivation.

4/7/19 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09958599 99217476

Immune restoration does not invariably occur following long-term **HIV-1 suppression** during antiretroviral **therapy**.

INCAS Study Group.
Pakker NG; Kroon ED; Roos MT; Otto SA; Hall D; Wit FW; Hamann D; van der Ende ME; Claessen FA; Kauffmann RH; Koopmans PP; Kroon FP; ten Napel CH; Sprenger HG; Weigel HM; Montaner JS; Lange JM; Reiss P; Schellekens PT; Miedema F
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AIDS (ENGLAND) Feb 4 1999, 13 (2) p203-12, ISSN 0269-9370
Journal Code: AID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

BACKGROUND: Current antiretroviral **treatment** can induce significant and sustained virological and immunological responses in **HIV-1** -infected persons over at least the short- to mid-term. OBJECTIVES: In this study, long-term immune reconstitution was investigated during highly active antiretroviral therapy. METHODS: Patients enrolled in the INCAS study in The Netherlands were treated for 102 weeks (range 52-144 weeks) with nevirapine (NVP) + zidovudine (ZDV) (n = 9), didanosine (ddI) + ZDV (n = 10), or NVP + ddI + ZDV (n = 10). Memory and naive CD4+ and CD8+ T cells were measured using CD45RA and CD27 monoclonal **antibodies** (mAb), T-cell function was assayed by CD3 + **CD28** mAb stimulation, and plasma HIV-1 RNA load was measured by ultra-direct assay (cut-off < 20 copies/ml). RESULTS: Compared to both double combination regimens the triple combination regimen resulted in the most sustained increase in CD4+ T cells (change in CD4+, + 253 x 10(6) cells/l; standard error, 79 x 10(6) cells/l) and reduction of plasma HIV-1 RNA. In nine patients (31%) (ddI + ZDV, n = 2; NVP + ddI + ZDV, n = 7) plasma HIV-1 RNA levels remained below cut-off for at least 2 years. On average, these long-term virological responders demonstrated a significantly higher increase of naive and memory CD4+ T cells (P = 0.01 and 0.02, respectively) as compared with patients with a virological failure, and showed improved T-cell function and normalization of the naive; memory CD8+ T-cell ratio. However, individual virological success or failure did not predict the degree of immunological response. T-cell patterns were independent of baseline CD4+ T-cell count, T-cell function, HIV-1 RNA load or age. Low numbers of naive CD4+ T cells at baseline resulted in modest long-term naive T-cell recovery. CONCLUSIONS: Patients with prolonged undetectable plasma **HIV-1** RNA levels during antiretroviral **therapy** do not invariably show immune restoration. Naive T-cell recovery in the setting of complete viral suppression is a gradual process, similar to that reported for immune recovery in adults after chemotherapy and bone marrow transplantation.

4/7/20 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09757952 99049855
Differential effects of CD28 costimulation on HIV production by CD4+ cells.
Barker E; Bossart KN; Levy JA
Department of Medicine, University of California, San Francisco 94143-1270, USA.
J Immunol (UNITED STATES) Dec 1 1998, 161 (11) p6223-7, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: RO1AI30350, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have observed that CD28 costimulation of CD4+ cells can have differential effects on HIV replication. Triggering the CD28 molecule on peripheral blood CD4+ cells during stimulation with anti-CD3 Abs enhances virus production following acute infection with HIV. Endogenous virus production in CD4+ cells from HIV-infected individuals is also increased by this procedure. The enhanced virus production occurs equally when anti-CD28 Abs and soluble forms of the natural ligands for CD28, CD80Ig, and CD86Ig are used to trigger CD28 on CD4+ cells during stimulation. This increased virus replication is observed only when the source of CD28 costimulation is removed immediately after stimulation and before infection. Continual exposure of CD4+ cells to anti-CD3 and CD28 Ab beads following acute infection **prevents** virus production. These findings may have relevance to **therapeutic** approaches aimed at **inhibiting** **HIV** replication by CD28 costimulation.

4/7/21 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09356551 98055739
DNA vaccination as anti-human immunodeficiency virus immunotherapy in infected chimpanzees.
Boyer JD; Ugen KE; Chattergoon M; Wang B; Shah A; Agadjanyan M; Bagarazzi ML; Javadian A; Carrano R; Coney L; Williams WV; Weiner DB
Department of Pathology, University of Pennsylvania School of Medicine, Philadelphia 19104, USA.
J Infect Dis (UNITED STATES) Dec 1997, 176 (6) p1501-9, ISSN 0022-1899 Journal Code: IH3
Contract/Grant No.: AI-93-21, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The role of the immune response in controlling human immunodeficiency virus type 1 (HIV-1) replication is controversial. Immunotherapeutic strategies that have the ability to broaden immune responses might play a role in slowing disease progression. DNA immunization was studied as immunotherapy in infected chimpanzees. Two HIV-1-infected chimpanzees were vaccinated with DNA plasmid vaccines, one with plasmid pCMN160, which expresses the envelope glycoprotein of HIV-1MN and rev, and the other with a control plasmid. The chimpanzee immunized with pCMN160 demonstrated enhanced humoral responses. Virus load was monitored. Virus load in the chimpanzee receiving pCMN160 decreased at week 20 and has remained at background levels. The control chimpanzee was subsequently vaccinated with pCMN160. After immunization, the antibody responses increased and, as in the first animal, the virus load decreased. These results indicate the potential of the immune response to have a direct impact on HIV-1 replication in chimpanzees.

4/7/22 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
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09296173 98031770
CD28 costimulation increases CD8+ cell **suppression** of **HIV** replication.
Barker E; Bossart KN; Fujimura SH; Levy JA
Department of Medicine, University of California School of Medicine, San Francisco 94143, USA.
J Immunol (UNITED STATES) Nov 15 1997, 159 (10) p5123-31, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: RO1AI30350, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A subset of CD8+ T lymphocytes that expresses CD28, a membrane receptor for B7 differentiation Ags found on APCs, is primarily responsible for the noncytotoxic **suppression** of HIV replication in CD4+ cells of HIV-infected individuals. Optimal **inhibition** of **HIV** production by CD8+ cells occurs after triggering the CD28 molecule on the cells with anti-CD28 Abs during stimulation. **Blocking** the interaction of the CD28 and B7 molecules with a CTLA4Ig fusion protein abrogates the ability of autologous macrophages to enhance this CD8+ cell antiviral activity. This blocking effect can be reversed by treating the CD8+ cells with anti-CD28 Ab. The increase in antiviral activity following CD28 costimulation correlates with enhanced IL-2 production and IL-2R expression by CD8+ cells. Prevention of IL-2 binding to its receptor, using anti-IL-2 or anti-IL-2R Abs, reduces the ability of CD8+ cells to suppress **HIV** replication following CD28 costimulation. Importantly, engagement of the CD28 molecule during stimulation of CD8+ cells from individuals with **AIDS** restored the ability of their cells to **suppress HIV** replication. Thus, triggering the CD28 molecule during stimulation of CD8+ cells could clinically benefit **HIV**-infected symptomatic patients.

4/7/23 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09266766 97287029
Protection of chimpanzees from high-dose heterologous HIV-1 challenge by DNA vaccination [see comments]
Boyer JD; Ugen KE; Wang B; Agadjanyan M; Gilbert L; Bagarazzi ML; Chattergoon M; Frost P; Javadian A; Williams WV; Refaeli Y; Ciccarelli RB; McCallus D; Coney L; Weiner DB
Department of Pathology, University of Pennsylvania, Philadelphia 19104, USA.
Nat Med (UNITED STATES) May 1997, 3 (5) p526-32, ISSN 1078-8956 Journal Code: CG5
Comment in Nat Med 1997 May;3(5):473
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Novel approaches for the generation of more effective vaccines for HIV-1 are of significant importance. In this report we analyze the immunogenicity and efficacy of an HIV-1 DNA vaccine encoding env, rev and gag/pol in a chimpanzee model system. The immunized animals developed specific cellular and humoral immune responses. Animals were challenged with a heterologous chimpanzee titered stock of HIV-1 SF2 virus and followed for 48 weeks after challenge. Polymerase chain reaction coupled with reverse transcription (RT-PCR) results indicated infection in the control animal, whereas those animals vaccinated with the DNA constructs were protected from the establishment of infection. These studies serve as an important benchmark for the use of DNA vaccine technology for the production of protective immune responses.

4/7/24 (Item 6 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
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08958039 97180871
Regulation of CD28 costimulation in human CD8+ T cells.
Lloyd TE; Yang L; Tang DN; Bennett T; Schober W; Lewis DE
Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas 77030, USA.
J Immunol (UNITED STATES) Feb 15 1997, 158 (4) p1551-8, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI36211, AI, NIAID; AI36682, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Optimal stimulation and **prevention** of anergy in T cells requires signaling through the CD28 molecule. During **HIV** disease progression, CD28 expression is lost, particularly on CD8+ T cells. Because alterations in cytokine production patterns occur during **HIV** infection, we determined whether CD8+ T cell phenotype or function was affected by cytokine environment. **Treatment** of CD8+ T cells with IL-4 decreased levels of both CD28 surface expression and message and increased CD8 expression. Furthermore, CD8+ T cells that had down-regulated CD28 had reduced proliferative capacity. The inhibitory effects of CD28 reduction could be compensated either by increased anti-CD3 or by exogenous IL-2, suggesting that the strength of T cell signaling necessary for the production of IL-2 and subsequent proliferation is negatively regulated by IL-4. CD8+ subpopulations with differential CD28 expression produced different patterns of cytokines, particularly IL-2 and IFN-gamma. Furthermore, CD8+ T cells that had reduced CD28 levels but made their own IL-2 were able to proliferate in response to TCR stimulation. These results suggest that loss of CD28 expression and CD8 T cell function can be regulated by the cytokine environment, which may be altered during HIV disease progression. Whether the dysfunction of CD8+ T cells in HIV infection occurs by such a mechanism is the subject of future investigation.

4/7/25 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08911776 97131728
Nuclear import of HIV-1 DNA in resting CD4+ T cells requires a cyclosporin A-sensitive pathway.
Sun Y; Pinchuk LM; Agy MB; Clark EA
Washington Regional Primate Research Center, University of Washington, Seattle 98195, USA.
J Immunol (UNITED STATES) Jan 1 1997, 158 (1) p512-7, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: RR00166, RR, NCRR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Using PCR to monitor early (LTR/LTR (long terminal repeat)) and late (LTR/gag) products of reverse transcription and the formation of HIV-1 LTR circles (indicating nuclear import), we explored the relationship between T cell activation signals and early events in the life cycle of HIV-1 infection. The combination of TCR ligation with either CD28 cross-linking or exogenous IL-2 was required for HIV-1 LTR circle formation in resting CD4+ T cells. Ligation of the TCR or CD28 receptors or addition of IL-2 alone did not induce this process. However, cross-linking the TCR, or IL-2 alone, unlike CD28 ligation, could induce the completion of viral reverse transcription. In contrast, the initiation of HIV-1 reverse transcription could occur in resting CD4+ T cells without any stimulation. Cyclosporin A (CsA), an **inhibitor** of T cell activation, completely **blocked** **HIV-1** DNA nuclear import in activated CD4+ T cells. The completion of **HIV-1** reverse transcription was **blocked** by CsA in infected CD4+ T cells activated by TCR ligation and IL-2, but not in

cells stimulated by TCR and CD28 ligation. The costimulation of CD3 and CD28 mAbs in the presence of IL-2 could not overcome the CsA inhibitory effect on nuclear import of viral DNA. Therefore, the factor(s) involved in a CsA-sensitive pathway plays a critical role in HIV-1 DNA transport from the cytoplasm into the nucleus. Production and movement of HIV-1 DNA in resting CD4+ T cells require two signals: one signal from the TCR, which normally regulates the G0 to G1 transition, induces completion of viral reverse transcription; the other signal through CD28 or an IL-2R-dependent process is sensitive to CsA treatment and regulates viral DNA entry into the nucleus.

4/7/26 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08730327 96280774
Selective CD4+ T cell deletion after specific activation in HIV-infected individuals; protection by anti-**CD28** monoclonal **antibodies**.
Cottrez F; Capron A; Groux H
Unite INSERM U167, Institut Pasteur, Lille, France.
Clin Exp Immunol (ENGLAND) Jul 1996, 105 (1) p31-8, ISSN 0009-9104
Journal Code: DD7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
AIDS is characterized by a progressive decline in the number of CD4+ T cells. This is preceded by an early selective defect in the proliferation of these cells to recall antigens [1-3], pokeweed mitogen (PWM) [4-6] and to superantigens (SAg) [4,7]. In contrast, the proliferative response to phytohaemagglutinin (PHA) remains intact [1,2,5]. We and others have shown that the proliferative defect in response to some stimuli was in fact due to the induction of cell death [4,7]. The activation-induced cell death mechanism that explains the proliferative defects observed in vitro might also account for the progressive in vivo deletion of CD4+ T cells. Indeed, studies performed on different models of primates have shown that induction of cell death in CD4+ T cells was detected only when T cells were isolated from animals infected with a type of retrovirus that induces an AIDS-like disease [8]. This correlation prompted us to analyse further the mechanism of HIV-induced activation cell death to determine the specificity and rate of induction of cell death. T cells from HIV-infected individuals were activated with superantigens and the V beta T cell receptor (TCR) expression analysed. Data presented here show that cell death is restricted to activated CD4+ T cells, and does not affect bystander cells. More importantly, addition of anti-CD28 MoAb specifically inhibited the induction of apoptosis, raising possibilities for therapy.

4/7/27 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08528293 96171633
N-acetylcysteine (NAC) enhances interleukin-2 but **suppresses** interleukin-4 secretion from normal and **HIV**+ CD4+ T-cells.
Eylar EH; Baez I; Vazquez A; Yamamura Y
Department of Biochemistry and Microbiology, Ponce School of Medicine, Puerto Rico 00732.
Cell Mol Biol (Noisy-le-grand) (FRANCE) 1995, 41 Suppl 1 pS35-40,
Journal Code: BNA
Contract/Grant No.: 1-S06-RR08239, RR, NCRR; 1-G-12RR03050, RR, NCRR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We find that purified CD4+ T cells from 30 **HIV**+ individuals have a **suppressed** Interleukin-4 (IL-4) production compared to normal controls regardless of activator (anti-CD3 or Con A) or co-activator [phorbol ester (PMA or anti-CD28)], generally by 2-4 fold. In every case,

the cells producing IL-4 respond more strongly to anti-CD28 co-activation than to PMA, ie, 1150 pg/ml compared to 2070 pg/ml for controls and 398 pg/ml compared to 125 pg/ml for HIV+ cells, respectively. In contrast, anti-CD3 with PMA gives a more vigorous IL-2 response than with anti-CD28, ie, 37.3 ng/ml compared to 12.3 ng/ml for controls and 28.5 ng/ml versus 15.1 ng/ml for HIV+ cells, respectively. These data are not compatible with the TH1/TH2 switch hypothesis since IL-4 production is decreased, not increased for CD4+ HIV+ T-cells and while IL-2 production is decreased with PMA, it is not decreased significantly with anti-CD28. Interestingly, 5 mM N-acetylcysteine (NAC) acts as an immunoenhancer; mitogenesis was enhanced 2 fold or more in general for control and HIV+ CD4+ T-cells and IL-2 production was enhanced 2-3 fold for anti-CD3 (with PMA or anti-CD28) for both controls and **HIV**+ CD4+ cells. However, NAC **suppressed** IL-4 production induced by anti-CD3 and anti-CD28 in both control and **HIV**+ CD4+ T cells. In the other cases, it produced in general no significant change.(ABSTRACT TRUNCATED AT 250 WORDS)

4/7/28 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08421893 95332751
HIV gp120 **inhibits** T cell activation by interfering with expression of costimulatory molecules CD40 ligand and CD80 (B71).
Chirmule N; McCloskey TW; Hu R; Kalyanaraman VS; Pahwa S
Department of Pediatrics, North Shore University Hospital-Cornell University Medical College, Manhasset, NY 11030, USA.
J Immunol (UNITED STATES) Jul 15 1995, 155 (2) p917-24, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI 28281, AI, NIAID; MO1 RR 0047, RR, NCRR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
One mechanism of the immune **suppression** in **HIV** infection has been postulated as being caused by the interaction of **HIV** envelope glycoprotein gp120 with CD4 molecules. Thus, pretreatment of purified peripheral blood T cells or CD4+ T cell clones with gp120 (or an anti-CD4 mAb) results in inhibition of anti-CD3 mAb-induced proliferative responses. In this study, we have analyzed the role of the interacting pairs of costimulatory molecules, CD28-B71 (CD80) and CD40 ligand (CD40L)-CD40, to elucidate further the mechanism of **HIV** gp120-induced **inhibitory** effects on T cell functions. Interactions between CD28-B71 and CD40L-CD40 were found to be essential for the anti-CD3 mAb-induced T cell proliferation, as demonstrated by up-regulation of B71 and CD40L and the ability of anti-B71 and anti-CD40L mAbs to inhibit this response. Pretreatment of CD4+ T cells with gp120 before CD3 ligation with anti-CD3 mAb resulted in failure of up-regulation of CD40L on T cells and B71 on APC. Exogenous addition of anti-CD28 mAb overcame the inhibitory effect of gp120 on anti-CD3 mAb-induced T cell proliferation. We conclude that binding of gp120 to CD4 molecules on T cells may interrupt the sequential cascade of intercellular interaction involving 1) Ag/MHC class II-TCR/CD4, 2) CD40L-CD40, and 3) B71-CD28. These studies indicate that the CD4-gp120 interaction results in dysregulation of expression of costimulatory molecules, CD40L, and B71 expression on T cells and APC, respectively, thereby contributing to the T cell hyporesponsiveness in HIV infection.

4/7/29 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05799418 89093961
Signaling through T lymphocyte surface proteins, TCR/CD3 and CD28, activates the HIV-1 long terminal repeat.
Tong-Starkesen SE; Luciw PA; Peterlin BM
Howard Hughes Medical Institute, Department of Medicine, San Francisco,

CA 94143.
J Immunol (UNITED STATES) Jan 15 1989, 142 (2) p702-7 ISSN 0022-1767
Journal Code: IFB
Contract/Grant No.: A125609
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The state of T cell activation and proliferation controls HIV-1 replication and gene expression. Previously, we demonstrated that the administration of PHA and PMA to the human T cell line Jurkat activates the HIV-1 enhancer, which is composed of two nuclear factor kappa B (NF kappa B) binding sites. Here, we show that PMA alone is sufficient for this effect. In addition, activation of T cells through the surface proteins TCR/CD3 and CD28 increased gene expression directed by the HIV-1 long terminal repeat (LTR) to the same extent as PMA. Analysis of 5' deletions in the LTR revealed that the NF kappa B binding sites and sequences in the upstream U3 region are required for this response. Whereas cyclosporin A did not inhibit the effect of PMA, it reduced the effects of agonists to TCR/CD3 and CD28 on the LTR. H7, an inhibitor of protein kinase C (PKC), blocked the effects of all stimuli. Thus, PMA activates the NF kappa B sites through a PKC-dependent pathway while ligands to TCR/CD3 and CD28 activate the LTR through a cyclosporin A-sensitive, PKC-dependent pathway of T cell activation. We conclude that mechanisms involved in the expression of IL-2 and the alpha-chain of the IL-2R alpha genes also play a role in the regulation of **HIV-1** . Physiologic stimuli can activate **HIV-1** gene expression; agents that **block** T cell activation also **inhibit** activation of the LTR. These observations might serve as a model for the regulation of **HIV-1** gene expression in peripheral blood T cells.

4/7/30 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

131101261 CA: 131(8)101261q PATENT
Methods of using human receptor protein 4-1BB
INVENTOR(AUTHOR): Kwon, Byoung S.
LOCATION: USA
ASSIGNEE: Advanced Research and Technology Institute, Inc.
PATENT: PCT International ; WO 9936093 A1 DATE: 19990722
APPLICATION: WO 99US823 (19990114) *US 7097 (19980114)
PAGES: 86 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A; A61K-038/17B; G01N-033/577B; C07K-016/28B; C12N-005/20B
DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE; CH; CY; DE ; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA215003 Immunochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: mouse human receptor protein 41BB antibody, cancer autoimmune disease AIDS monoclonal antibody
DESCRIPTORS:
TCR(T cell receptors)...
activation; agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS
AIDS(disease)... Antibodies... Antitumor agents... Apoptosis... Autoimmune diseases... B cell activation... B cell proliferation... cDNA... CD28(antigen)... CD3(antigen)... CD4-positive T cell... CD8-positive T cell ... Cytokines... Diabetes mellitus... DNA sequences... Fluorescence microscopy... Human immunodeficiency virus 1... Hybridomas... IgG1... IgG2 ... Interferon .gamma.... Interleukin 10... Interleukin 1... Interleukin 2 ... Intravenous injections... Monoclonal antibodies... Oral drug delivery systems... Protein sequences... Rheumatoid arthritis... Scintillation detectors... Systemic lupus erythematosus... T cell activation... T cell proliferation... Tablets(drug delivery systems)... Th1 cell... Th2 cell... Transplant rejection... Transplant(organ)...

agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

Cytokines...
B-cell differentiation factor; agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

Cytokines...
B-cell growth factor; agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

Microglia...
HIV-1-infected cells; agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

Astrocyte... Dendritic cell... Macrophage...
HIV-1-infected; agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

Ligands... Receptors...
H4-1BB; agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

CAS REGISTRY NUMBERS:

9001-78-9 agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

125266-94-6 153551-41-8 amino acid sequence; agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

230626-69-4P H4-1BB contg.; agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

230974-87-5 230974-88-6 nucleotide sequence; agonistic and antagonistic monoclonal antibodies to human receptor protein 4-1BB for treating autoimmune diseases, cancer, transplant rejection, and AIDS

4/7/31 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130037308 CA: 130(4)37308k PATENT
Human CD28 specific monoclonal antibodies for antigen non-specific activation of T-lymphocytes

INVENTOR(AUTHOR): Hunig, Thomas; Tacke, Michael; Hanke, Thomas; Hanke, Gabriele; Hara, Toyomichi; Rodriguez-Palmero, Marta
LOCATION: Germany,

PATENT: PCT International ; WO 9854225 A2 DATE: 19981203
APPLICATION: WO 98DE1499 (19980528) *DE 19722888 (19970528)
PAGES: 41 pp. CODEN: PIXXD2 LANGUAGE: German CLASS: C07K-016/00A
DESIGNATED COUNTRIES: AL; AM; AU; BA; BB; BG; BR; BY; CA; CN; CU; CZ; EE; GE; HU; ID; IL; IS; JP; KG; KP; KR; KZ; LK; LR; LT; LV; MD; MG; MK; MN; MX; NO; NZ; PL; RO; RU; SG; SI; SK; TJ; TM; TR; TT; UA; US; UZ; VN; YU
DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG
SECTION:
CA215003 Immunochemistry

IDENTIFIERS: monoclonal antibody CD28 T lymphocyte immunotherapy disease

DESCRIPTORS:

T cell infection...
CD4-pos. T cell; human CD28-specific monoclonal antibodies for antigen non-specific activation of T-lymphocytes and their use in disease therapy

AIDS(disease)... Allergies... Allograft... Antigens... Autoimmune diseases

... B cell hybridoma... Body fluid... cDNA... CD28(antigen)... CD4-positive T cell... Chemokines... Chemotherapy... Contact dermatitis... Cytokines... Escherichia coli... Genetic analysis(animal)... Hematopoietic stem cells... Human immunodeficiency virus 1... Immunization... Immunostimulation... Immunotherapy... Inflammatory bowel diseases... Insulin dependent diabetes mellitus... Interleukin 10... Interleukin 4... Leukemia... Monoclonal antibodies... Mouse... Multiple sclerosis... Plasmid vectors... Polyoxyalkylenes,biological studies... Protoplast... Rheumatoid arthritis ... T cell activation... T cell proliferation... T cell(lymphocyte)... TCR(T cell receptors)... Th1 cell... Th2 cell... Tumors(animal)...
human CD28-specific monoclonal antibodies for antigen non-specific activation of T-lymphocytes and their use in disease therapy
CD4-positive T cell...
infection; human CD28-specific monoclonal antibodies for antigen non-specific activation of T-lymphocytes and their use in disease therapy
CAS REGISTRY NUMBERS:
25322-68-3 human CD28-specific monoclonal antibodies for antigen non-specific activation of T-lymphocytes and their use in disease therapy

4/7/32 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

122185363 CA: 122(15)185363z PATENT
Methods for selectively stimulating proliferation of T cells
INVENTOR(AUTHOR): June, Carl H.; Thompson, Craig B.; Nabel, Gary J.; Gray, Gary S.; Rennert, Paul D.
LOCATION: USA
ASSIGNEE: United States Dept. of the Navy; Regents of the Univeristy of Michigan; Repligen Corp.
PATENT: PCT International ; WO 9429436 A1 DATE: 941222
APPLICATION: WO 94US6255 (940603) *US 73223 (930604)
PAGES: 70 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-005/08A; A61K-035/14B; C12N-005/20B; C12P-021/08B; A61K-037/02B
DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE; CH; DE; DK ; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA215010 Immunochemistry
IDENTIFIERS: monoclonal antibody CD3 CD28 T cell, CD2 TCR T cell activation
DESCRIPTORS:
Ionophores...
calcium; T cell activation by; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
Antibodies,monoclonal... Antigens,CD28... Hematopoiesis,leukopoiesis... Hematopoiesis,T-cell lymphopoiesis... Neoplasm inhibitors... Virus,animal, human immunodeficiency...
CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
Lymphocyte,T-cell...
CD4+ or CD8+; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
Antigen receptors,TCR (T-cell antigen receptor)... Receptors,TCR (T-cell antigen receptor)...
complexes with CD3; T cell activation; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
Antigens,CD3...
complexes with T cell receptor; T cell activation; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer

Protein sequences...
of immunogenic epitope of CD28; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
Antigens,CD2...
T cell activation; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
Immunodeficiency...
T cells derived from patients with; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
CAS REGISTRY NUMBERS:
141436-78-4 activator; T cell activation by; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
161704-47-8D 161704-48-9D Cys, Ile, Leu, Arg, Pro substitutes, immunogenic epitope of CD28 or anti-CD28 antibody binding to; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
161622-45-3 161622-46-4 161622-47-5 161622-48-6 161622-49-7 161622-50-0 161622-51-1 161622-52-2 161622-53-3 161622-54-4 161622-55-5 161622-56-6 161622-57-7 161622-58-8 161622-59-9 161622-60-2 immunogenic epitope of CD28 or anti-CD28 antibody binding to; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer
7440-70-2 miscellaneous, ionophore; T cell activation by; CD4+ or CD8+ T cells stimulated by anti-CD3 and anti-CD28 antibodies for use in immunotherapy or diagnosis of HIV infection and cancer

4/7/33 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0234068 DBA Accession No.: 99-04169
Green fluorescent protein as a selectable marker of fibronectin-facilitated retroviral gene transfer in primary human T-lymphocytes - retro virus-mediated gene transfer allowing monitoring of transfection without cytotoxicity, useful in optimization of cancer, **AIDS** and single gene disorder gene **therapy** protocols
AUTHOR: Dardalhon V; +Noraz N; Pollok K; Rebouissou C; Boyer M; Bakker A Q; Spits H; Taylor N
CORPORATE AFFILIATE: Univ.Montpellier CNRS Riley-Child.Hosp.Indianapolis Univ.Indiana Netherlands-Cancer-Inst.
CORPORATE SOURCE: Institut de Genetique Moleculaire de Montpellier, CNRS UMR 5535, 1919 Route de Mende, 34033 Montpellier, Cedex 1 France.
JOURNAL: Hum.Gene Ther. (10, 1, 5-14) 1999
ISSN: 1043-0342 CODEN: HGTHE3
LANGUAGE: English
ABSTRACT: The ability to monitor retro virus marked cells is an important prerequisite for gene transfer. Transductions of primary human T-lymphocytes were carried out using cell-free supernatants from a PG13 packaging cell culture in which a retro virus expressing enhanced green fluorescent protein (EGFP) was pseudotyped with the gibbon ape leukemia virus (GALV) envelope. A 726 bp sequence encoding EGFP was cloned downstream of the internal ribosomal entry site in the LZRS retro virus vector, using a plasmid pBluescript, as an NcoI/NotI fragment. This was combined with a fibronectin-facilitated protocol, primary lymphocytes were transduced with an average gene transfer efficiency of 27.5% after a 2 day mitogen stimulation with either PHA or anti-CD3/**CD28** **antibodies** . Factors other than proliferation were found to be important for optimal retro virus-mediated gene transfer. This work demonstrated the usefulness of EGFP, which lacks cytotoxicity, as a selectable marker for human T-lymphocyte transduction and enables

further optimization of T-lymphocyte gene **therapy** regimes for **treating** e.g cancer, **AIDS** and single gene disorders (43 ref)

4/7/34 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0232068 DBA Accession No.: 99-02169 PATENT
Monoclonal antibodies compatible with humans - monoclonal antibody used to activate T-lymphocytes to enhance the immune system response
AUTHOR: Huenig T; Tacke M; Hanke T; Hanke G; Rodriguez-Palmero M
CORPORATE SOURCE: Wuerzberg, Germany.
PATENT ASSIGNEE: Huenig T 1998
PATENT NUMBER: DE 19722888 PATENT DATE: 981203 WPI ACCESSION NO.: 99-025648 (9903)
PRIORITY APPLIC. NO.: DE 1022888 APPLIC. DATE: 970528
NATIONAL APPLIC. NO.: DE 1022888 APPLIC. DATE: 970528
LANGUAGE: German
ABSTRACT: Monoclonal **antibodies** that are compatible with humans, and specific for human **CD28** are claimed. The **antibodies** are capable of activating T-lymphocytes, non-antigen specifically. These **antibodies** are used to prepare medication, and in disease **therapy** , particularly of diseases that cause pathologically low CD4 T-cell count, such as **AIDS**, or as a result of stem cell transplantation or chemotherapy. The antibodies potentiate and qualitatively influence the immune reaction in vaccinations, and effect the quality of T-lymphocyte reactions. This is especially for use in enhancing the production of different effector molecules such as cytokines in autoimmune diseases. The **antibodies** are prepared by hybridoma cell culture, using **CD28** human or animal antigens. They can also be prepared recombinantly by transfecting cells with plasmids that contain CD28 cDNA. This makes use of vector plasmid pH-beta-APr-1-neo, following excision of that plasmid's SalI-HindIII fragment. (10pp)

4/7/35 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0231505 DBA Accession No.: 99-01606
T cell activation modulates retro virus-mediated gene expression - retro virus vector-mediated interleukin-1-beta gene transfer to human T-lymphocyte for e.g. cancer, **AIDS** and adenosine-deaminase deficiency gene **therapy**
AUTHOR: Quinn E R; Lum L G; +Trevor K T
CORPORATE AFFILIATE: St.Luke's-Med.Cent.Milwaukee Univ.Wayne-State
CORPORATE SOURCE: Immunotherapy Research and Treatment Institute, St. Luke's Medical Center, 2900 W. Oklahoma Avenue, Milwaukee, WI 53201, USA.
JOURNAL: Hum.Gene Ther. (9, 10, 1457-67) 1998
ISSN: 1043-0342 CODEN: HGTHE3
LANGUAGE: English
ABSTRACT: Retro virus vector-mediated gene transfer and the fate of proviral gene expression were evaluated in human T-lymphocytes activated using immobilized anti-CD3 monoclonal **antibody** (MAb) plus interleukin-2, or cis costimulation using beads carrying coimmobilized anti-CD3 and anti-**CD28** MAbs. By crosslinking the CD3 and CD28 receptors, these MAbs mimic in vivo signaling events, leading to cytokine production and proliferation. A modified human interleukin-1-beta cDNA inserted into the MFG retro virus vector served as an indicator gene. Early after MAb stimulation and virus exposure, proviral gene expression was greater at the RNA and protein levels in optimized anti-CD3/anti-CD28 bead-activated T-lymphocytes,

corresponding with augmented endogenous cytokine responses and mitogenesis. Provira[redacted]gene regulation was downregula[redacted] in the absence of T-lymphocyte si[redacted]ling events and has implica[redacted]ns for clinical strategies using retro virus vector-modified T-lymphocytes. The above may be used for e.g. cancer, **AIDs** and adenosine-deaminase deficiency gene **therapy**. (52 ref)

4/7/36 (Item 4 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0205745 DBA Accession No.: 97-00866 PATENT
Improving transfection of T cells by preliminary costimulation of proliferating cells - primary T-lymphocyte transfection method for **HIV** virus infection and autoimmune disease gene **therapy**
AUTHOR: June C H; Thompson C B; Kim S
CORPORATE SOURCE: Bethesda, MD, USA; Ann Arbor, MI, USA.
PATENT ASSIGNEE: U.S.Navy; Univ.Michigan 1996
PATENT NUMBER: WO 9634970 PATENT DATE: 961107 WPI ACCESSION NO.: 96-506172 (9650)
PRIORITY APPLIC. NO.: US 475136 APPLIC. DATE: 950607
NATIONAL APPLIC. NO.: WO 96US6200 APPLIC. DATE: 960502
LANGUAGE: English
ABSTRACT: A method for improving primary T-lymphocyte transfection is new. T-lymphocytes are transfecting by contacting proliferating cells with at least one costimulatory agent (I) then introducing DNA (II) containing the gene to be expressed in the proliferating, stimulated cells. Cells are contacted with an agent that stimulates proliferation and then with a mixture of a compound (Ia) that provides a primary activation signal and an agent (Ib) that provides a costimulatory signal. The treatment is for 1-24 hr (especially 10 hr) before the introduction of (II). (Ia) interacts with a T-lymphocyte cell receptor/CD3 complex (anti-CD3 **antibody**), with a CD2 molecule on the cells or is an antigen on an antigen-presenting cell. (Ib) is an anti-**CD28 antibody**, or stimulatory form of a natural ligand of **CD28** (especially the B-lymphocyte antigens B7-1 or -2). Alternatively, (I) is a combination of a phorbol ester and calcium ionophore, a protein-tyrosine-kinase (EC-2.7.1.112) or a superantigen. (II) may encode a protein, an antisense RNA or ribozyme. Such a method may be used for **HIV** virus infection and autoimmune disease gene **therapy**. (54pp)

4/7/37 (Item 5 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0175838 DBA Accession No.: 95-02659 PATENT
Method for inducing the proliferation of T-cells - T-lymphocyte proliferation using CD3 and **CD28**-specific monoclonal **antibody**, application in HIV virus infection immunotherapy and diagnosis
AUTHOR: June C H; Thompson C B; Nabel G J; Gray G S; Rennert P
PATENT ASSIGNEE: U.S.Navy; Univ.Michigan; Repligen 1994
PATENT NUMBER: WO 9429436 PATENT DATE: 941222 WPI ACCESSION NO.: 95-036466 (9505)
PRIORITY APPLIC. NO.: US 73223 APPLIC. DATE: 930604
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LANGUAGE: English
ABSTRACT: The following are claimed: (1) a method for inducing a population of T-lymphocyte (TL) to proliferate by activating a population of TLs, and stimulating an accessory molecule on the surface of the TLs with a ligand which binds the accessory molecule; (2) a substantially homogeneous CD4+ TL cell population produced by (1); (3) a hybridoma designated ATCC HB11373; (4) a monoclonal antibody (MAb) produced by

(3); (5) a substantially homogeneous CD8+ TL cell population produced by (1); (6) a MAb which specifically binds an accessory molecule having a mol.wt. of 27,000 present on activated TLs; (7) a hybridoma designated ATCC HB11374; (8) a MAb produced by (7); and (9) a peptide composed of a specified protein sequence. Preferably, the TLs are rendered resistant to **HIV** virus infection by contacting the TLs with at least 1 anti-retro virus agent which **inhibits HIV** virus replication or viral production. The anti-CD3 **antibody** OKT3 and the anti-**CD28 antibody** 9.3 or EX5.3D10, and monoclonal **antibody** ES5.2D8 may be used in (1). The TL population may be genetically transduced and used for immunotherapy or diagnosis. (71pp)

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New B7 antigen ligand reactive with T-lymphocyte CD28 receptor - fusion protein and monoclonal antibody; application to therapy of e.g. graft versus host disease, lymphoma, etc.
PATENT ASSIGNEE: Bristol-Myers-Squibb 1992
PATENT NUMBER: WO 9200092 PATENT DATE: 920109 WPI ACCESSION NO.: 92-041351 (9205)
PRIORITY APPLIC. NO.: US 722101 APPLIC. DATE: 910627
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ABSTRACT: The following are claimed: a method for regulating functional T-lymphocyte responses comprising contacting CD28-positive cells with a ligand for the CD28 receptor; B7Ig fusion protein reactive with the CD28 receptor comprising amino acids 1-215 of the extracellular domain of the B7 antigen, a hinge region, and the CH2 and CH3 regions of human immunoglobulin Cgamma1, and corresponding to the amino acid sequence encoded by DNA (ATCC 68627); a monoclonal antibody, Mab BB-1, reactive with fusion protein B71g; CD28Ig fusion protein reactive with the B7 antigen comprising amino acids 1-134 of the extracellular domain of the CD28 receptor, a hinge region, and CH2 and CH3 regions of human IgCgamma1, and corresponding to the amino acid sequence encoded by DNA (ATCC 68628); and MAb 9.3 reactive with the CD28Ig fusion protein, and produced by hybridoma ATCC HB-10271. The new reagents and methods can be used for modulating T-lymphocyte activity to treat pathological conditions such as autoimmunity, transplant rejection, infectious diseases and neoplasia. They can be used to **treat** e.g. lymphoma, carcinoma, leukemia, graft versus host disease, **AIDS**, etc. (106pp)